

REMARKS

This Amendment and Remarks are filed in response to the Office Action dated November 29, 2007. Claims 31-42 are pending and are free of the prior art but are subject to 35 USC 112, second paragraph and double patenting rejections.

Claim Rejections - 35 use § 112

Claims 31-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Examiner argues that claim 31 is confusing and unclear by the preamble requiring "repair of damaged, injured, diseased or aged articular cartilage and cartilage lesions", and steps d)-f) being drawn only to repair of a lesion by requiring pre-treating a lesion by depositing a bottom sealant in the lesion, implanting a construct into the lesion and depositing a top sealant over the implanted construct. It does not appear steps d)-f) can be performed when a lesion is not repaired as encompassed by the preamble.

It is suggested the preamble be amended by canceling "damaged, injured, diseased or aged articular cartilage" to direct the preamble to repairing a cartilage lesion as required in steps d)-f).

In line 2 of step c) of claim 31, it would be uncertain as to how the construct differs from the support matrix since steps of preparing the construct comprising the support matrix have not been recited. It is suggested "a construct comprising" in line 2 of step c) be deleted.

In line 2 of step c), "of step (a)" is confusing since the seeded support matrix from step b) is used in step c). It is

suggested "of step (a)" be replaced with ---from step (b)---.

In line 3 of step c), "suspension of step (b)" is confusing since step (b) is not directed to producing a suspension. It is suggested line 3 be amended by changing "chondrocyte" to ---chondrocytes--- and cancel "suspension of step (b)".

In lines 18-19 of claim 31, requiring hydrostatic pressure to be applied at about 0.01 to about 2.0 Hz is confusing since a constant frequency. It is suggested "and is applied at from about 0.01 to about 2.0 Hz" (bridging, lines 18 and 19) be deleted. If desired, the frequency can be claimed in a dependent claim further limiting the cyclic hydrostatic pressure as in claims 37 and 38.

Applicants appreciate Examiner's suggestions and amended Claim 31, after due consideration, as suggested.

Claim 36 is confusing by not having clear antecedent basis for "the Type I or Type II collagen sponge, honeycomb, scaffold or a honeycomb-like lattice" since a previous claim does not require a Type I or Type II collagen sponge, a honeycomb, a scaffold or a honeycomb-like lattice. Claim 31 requires a porous sponge, porous scaffold, porous honeycomb or porous honeycomb-like lattice. Additionally, the honeycomb, scaffold and honeycomb-like lattice in claim 36 are already required in claim 31. It is suggested claim 36 be amended by canceling lines 2-3, and in place thereof insert ---porous sponge, porous scaffold, porous honeycomb or porous honeycomb-like lattice is prepared from a material selected from the group consisting of Type I collagen and Type II collagen---.

Applicants amended claim 36 as suggested.

In line 2 of claim 39, "construct" is confusing for reasons set forth above in regard to "construct" recited in line 2 of step c)

of claim 31. It is suggested "construct comprising said" be deleted.

Claim 39 is amended as recommended.

The recital of "construct" in line 2 of claim 41 is confusing for reasons set forth above in regard to "construct" in claims 31 and 39.

Claim 41, is further confusing by not having clear antecedent basis for "said derivatized polyethylene glycol cross-linked with methylated collagen top sealant". Derivatized polyethylene glycol cross-linked with methylated collagen has not been previously required as a top sealant.

In line 6, claim 41 is unclear as to how "(superficial cartilage layer)" limits the method since this layer appears to be the same as the layer required in line 5. Bridging lines 6 and 7, claim 41 is confusing by not having clear antecedent basis for "the layer of the second sealant". A layer of second sealant has not been previously required. It is suggested claim 41 be amended as follows:

line 1, cancel "a", line 2, cancel "combination of said construct deposited into said lesion and", line 3, before "derivatized" insert ---top sealant is---, line 4, cancel "top sealant deposited over said construct" and insert ---and---, line 6, cancel "(superficial cartilage layer)", and cancel "layer of" and insert ---top sealant---, and line 7, cancel "the second sealant".

Applicants amended claim 41 and also claim 33 to specifically list the derivatized polyethylene glycol cross-linked with methylated collagen.

With the amendment of claims 31, 33, 36 , 39 and 41, the rejection under 35 USC 112, second paragraph is overcome and claims are in allowable conditions.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998) *In re Goonan*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993) *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985) *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982) *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 25 1.321<sup>©</sup> or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31-38, 41 and 42 are rejected on the ground of

nonstatutory obviousness-type, double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 7,217,294 in view of Smith et al (6,528,052).

The patent claims require a method as presently claimed except that the matrix implanted-in a cartilage lesion is not seeded with chondrocytes and subjected to a constant or cyclic hydrostatic pressure followed by a resting period before implanting as claimed. Smith et al disclose a method for in vivo, ex vivo or in vitro repair and regeneration of cartilage. The cartilage can be articular cartilage (col I, line 42): In vitro treatment is performed by obtaining cartilage cells from cartilage, applying an interval loading regiment while culturing the cartilage cells in suspension within a scaffold/support, and implanting the resultant tissue or cells into a patient (col 9, lines 23-30, and col 11, lines 5-9). The interval loading regiment involves treatment of cartilage or cartilage cells by using conditions of intermittent application of periods of hydrostatic pressure followed by periods of recovery (col 4, lines 25-31, and col 7, line 30 to col 8, line 8). The recovery period can be at atmospheric or low constant pressure (col 7, lines 48-50).

Examiner argues that it would have been obvious to seed the matrix of the patent claims with chondrocytes, and subject the seeded matrix to hydrostatic pressure and a recovery period as suggested by Smith et al to provide cells or tissue in the matrix for implanting. Specific condition of dependent claims would have been matters of obvious choice in view of conditions of the patent claims and disclosed by Smith et al.

Applicants disagree. The instant claims are directed to a method for treatment of cartilage lesions by preparing a viable

fully cellularized support matrix containing isolated cells, activating said cells within said matrix by applying hydrostatic pressure and implanting such matrix into the lesion. The lesion is protected by two layers of a sealant placed at the bottom and on the top of the lesion. Difference between the instant claims and those of Smith is that the instant support matrix containing the cell is activated as a whole construct whereas in the Smith's claims, the cells are first activated, then loaded into a scaffold/support and then implanted (see claims 1, 7, 9 and 11). Further, Smith does not utilize any sealant at all.

Patent No. 7,217,294 ('294) claims acellular (empty) matrix without any cells at all being implanted into a cartilage lesion where a first bottom sealant is deposited at the bottom of the lesion and the second top sealant is deposited on the top of the implanted matrix.

Both the '294 patent and Smith reference use an untreated support matrix whereas the instant support matrix is treated with cells being seeded within the matrix before the hydrostatic pressure treatment.

Applicants respectfully submit that the instant claims, as amended, are patentable and not subject to double patenting rejections. However, in the interest of the expedited prosecution and allowance of the claims, Applicants herein enclose the fully executed Terminal Disclaimer with respect to the patent 7,217,294.

Examiner further rejects Claim 39 on the ground of nonstatutory obviousness-type double patenting as set forth above in regard to claims 31-38, 41 and 42, and further in view of Nevo et al (6,632,651).

Claim 39 requires the matrix seeded with chondrocytes to be perfused with a medium at a flow rate from about 1  $\mu$ L/min to about

500  $\mu\text{L}/\text{min}$ .

Nevo et al disclose perfusing cells with a medium to maintain viability and growth prior to implanting (col 2, lines 8-15 and col 8, lines 41-43).

When seeding the matrix of the patent claims with chondrocytes and subjecting the seeded matrix to hydrostatic pressure as set forth above, it would have been obvious to perfuse the seeded matrix with a culture medium to maintain viability and growth of the cells as suggested by Nevo et al.

Selecting a preferred flow rate of about 1  $\mu\text{L}/\text{min}$  to about 500  $\mu\text{L}/\text{min}$  would have been obvious to maintain preferred optimum viability and growth of cells.

Applicants disagree. It has been shown above that the instant claims differ from both the '294 patent and Smith reference and are not subject to double patenting. Applicants submit that, consequently, the matrix seeded with cells and treated according to the disclosed method with a hydrostatic pressure and at the same time submitted to a perfusion would not have been obvious from the reference that is directed to maintaining a viable tissue.

Moreover, the patent No.: 7,217,294 is being disclaimed.

Examiner additionally rejects Claim 40 on the ground of nonstatutory obviousness-type double patenting as set forth above in regard to claims 31-38, 41 and 42, and further in view of Hungerford et al (6,378,527).

The claim requires perfusion at a flow rate in a range of about 5  $\mu\text{L}$  to about 50  $\mu\text{L}$  and in the presence of about 1% to about 20% oxygen.

Examiner maintains that Hungerford et al disclose that using a low oxygen level of about 5% when culturing chondrocytes seeded on a scaffold results in enhanced expression of collagen type II and

aggrecan, as well as helping maintain chondrocyte phenotype (col 24, lines 14-23).

When seeding the matrix of the patent claims with chondrocytes and subjecting the seeded matrix to hydrostatic pressure as set forth above, it would have been obvious to use an oxygen level of about 5% when culturing chondrocytes in the matrix to obtain enhanced expression of collagen type II and aggrecan, as well as help maintain chondrocyte phenotype as suggested by Hungerford et al. The perfusion flow rate would have been obvious for reasons set forth above.

Applicants disagree. The perfusion flow, by itself, whether in the presence of low oxygen or not does not make the instant claims obvious for the purposes of the double patenting obviousness rejections. Moreover, as pointed out above, the patent 7,217,294 is disclaimed.

Applicants submit that the obviousness double patenting rejection is overcome and request Examiner to withdraw this rejection and to pass the claims to issue.



3831.09

PATENT


Serial No.: 10/625,822

SUMMARY

In summary, claims are amended to overcome rejections under 35 USC 112, second paragraph. Terminal Disclaimer is submitted together with arguments to overcome Obviousness Double Patenting rejections. It is believed that all claims are in conditions for allowance. Notice of Allowance is respectfully requested.

Respectfully submitted,

Date: February 26, 2008

  
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